IARC Reevaluates Silica and Related Substances

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An IARC working group of 19 experts in chemical carcinogenesis and seven industrial or governmental observers met in October 1996 in Lyon to prepare updated monographs and evaluations on crystalline and amorphous silica, palygorskite (attapulgite), sepiolite, and wollastonite. Monographs on these agents were published previously in Volume 42 of the *IARC Monographs* (*1*). Also evaluated by the group were some natural and synthetic zeolites (excluding erionite), coal dust, and the organic fibers *para*-aramid fibrils. Erionite, a fibrous component of some natural zeolite deposits in various parts of the world, was evaluated previously as being carcinogenic to humans (Group 1) in Volume 42 and Supplement 7 of the *IARC Monographs* (*1,2*).

Silica

Silica occurs in crystalline and amorphous forms. Human exposure to respirable crystalline silica (mainly in the form of quartz, cristobalite, and tridymite) occurs in a wide variety of industries and occupations. Very few data are available on exposures to crystalline silica in nonoccupational circumstances. Respirable quartz levels are frequently found in metal and nonmetal mines, coal mining, granite quarrying and processing, crushed stone and related industries, foundries, ceramics industries, and in construction and sandblasting operations. Cristobalite is formed from quartz at temperatures above 1400°C and from some amorphous silica (e.g., diatomaceous earth) at temperatures above 800°C. Amorphous silica occurs as diatomaceous earth and as biogenic silica in some plants. Synthetic amorphous silicas are produced as pyrogenic (fumed) silica, precipitated silica, and silica gel.

Evaluation of the carcinogenicity of crystalline silica in humans pertains to inhalation resulting from workplace exposures, and the primary focus was on lung cancer. Inhalation of crystalline silica implies the deposition of particles of about 2–5 µm aerodynamic diameter in the alveolar region of the lungs.

Possible differences in carcinogenic potential among polymorphs of crystalline silica were considered. Some studies were of populations exposed principally to quartz. In only one study of U.S. diatomaceous earth workers was the exposure predominantly to cristobalite. Studies of mixed environments (i.e., ceramics, pottery, refractory brick) could not delineate exposures specifically to quartz or cristobalite. Exposure to coal and coal mine dust also entails exposures to silica. Although there were some indications that cancer risks varied by type of industry and process in a manner suggestive of polymorph-specific hazards, the working group could only reach a single evaluation for quartz and cristobalite.

For the evaluation of crystalline silica, the following epidemiological studies provided the least confounded examinations of an association between silica exposure and cancer risk: South Dakota gold miners (*3–5*), Danish stone industry workers (*6*), Vermont granite shed and quarry workers (*7*), U.S. crushed-stone industry workers (*8*), U.S. diatomaceous earth industry workers (*9,10*), Chinese refractory brick workers (*11*), Italian refractory brick workers (*12*), United Kingdom pottery workers (*13–18*), Chinese pottery workers (*19,20*), and cohorts of registered silicotics from North Carolina (*21*) and Finland (*22*). With the exception of the U.S. studies on gold miners, these studies demonstrated excess lung cancer risks in exposed populations. However, in view of the relatively large number of epidemiological studies that have been undertaken and given the wide range of populations and exposure circumstances studied, some nonuniformity of results would be expected. In some studies, increasing risk gradients have been observed in relation to dose surrogates—cumulative exposure, duration of exposure, or the presence of radiographically defined silicosis—and, in one instance, to peak intensity exposure. For these reasons, the working group concluded that, overall, the epidemiological findings support increased lung cancer risks from inhaled crystalline silica (quartz and cristobalite) resulting from occupational exposure. The observed associations could not be explained by confounding or other biases.

Very little epidemiological evidence was available to the working group on amorphous silica. No association was detected for mesothelioma with biogenic amorphous silica fibers in the three community-based case–control studies (*23–25*). Separate analyses were not performed for cancer risks among a subset of diatomaceous earth industry workers exposed predominantly to amorphous silica (*9*).

The working group concluded that there is sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the forms of quartz or cristobalite from occupational sources. There is inadequate evidence in humans for the carcinogenicity of amorphous silica. No epidemiological studies on environmental exposures to crystalline silica were available to the working group.

Studies in rodents have been conducted with different specimens of quartz with particle sizes in the respirable range. In eight experiments in rats by inhalation exposure or by intratracheal instillation, there were significant increases in the incidence of adenocarcinomas and squamous-cell carcinomas of the lung; marked dense pulmonary fibrosis was an important part of the biological response. Pulmonary granulomatous inflammation and slight to moderate fibrosis of the alveolar septa but no pulmonary tumors were observed in Syrian hamsters in three experiments using repeated intratracheal instillation of quartz dusts. No increase in the incidence of lung tumors was seen with one sample of quartz in the strain A mouse lung adenoma assay and with another quartz sample in an inhalation study in mice using small numbers of animals and variable exposure periods; granulomas containing silica particles and lymphoid cuffing around airways were seen in the lungs of quartz-treated mice, but no fibrosis occurred.

In seven studies in rats using single intrapleural or intraperitoneal injections of suspensions of several types of quartz, thoracic and abdominal malignant lymphomas (primarily of the histiocytic type) were found. Intrapleural injection of cristobalite and tridymite with particles in the respirable range also resulted in malignant lymphomas (primarily of the histiocytic type) in three studies in rats.

Mechanistic evidence suggests that the development of lung tumors in rats in response to crystalline silica (quartz) is the result of marked and persistent inflammation and epithelial proliferation; however, a role for surface-generated oxidants or even a direct genotoxic effect cannot be ruled out.

The working group concluded that there is sufficient evidence in experimental animals for the carcinogenicity of quartz

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and cristobalite; there is limited evidence in experimental animals for the carcinogenicity of tridymite; there is inadequate evidence in experimental animals for the carcinogenicity of uncalcined diatomaceous earth; and there is inadequate evidence in experimental animals for the carcinogenicity of synthetic amorphous silica.

In making the overall evaluation, the working group noted that carcinogenicity in humans was not detected in all industrial circumstances studied. Carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs. The final conclusion based upon all the available data was that crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is carcinogenic to humans (Group 1) and that amorphous silica is not classifiable as to its carcinogenicity to humans (Group 3).

Silicates

Among the other agents evaluated by the working group were some fibrous silicate minerals. Palygorskite (attapulgite) is a hydrated magnesium aluminum silicate that occurs as a fibrous chain–structure mineral in clay deposits in several areas of the world. Palygorskite fiber characteristics vary with the source, but fiber lengths in commercial samples are generally less than 5 µm. Palygorskite has been mined since the 1930s and is used mainly as an adsorbent for pet wastes and oils and greases and as a component of drilling muds.

Sepiolite is a hydrated magnesium silicate that occurs as a fibrous chain–structure mineral in clays in several areas of the world, with the major commercial deposits occurring in Spain. Sepiolite fiber characteristics vary with the source, but the fiber lengths in commercial samples are generally less than 5 µm. Sepiolite has been mined since the 1940s, finding its greatest use as an adsorbent, particularly for pet waste and oils and greases. It is also used as a drilling mud.

Wollastonite is a calcium silicate mineral that occurs naturally in deposits in several areas of the world. It has been mined in commercial quantities since the 1950s. Wollastonite breaks down during processing (crushing and grinding) into fibers of varying aspect ratios. High-aspect ratio wollastonite (length:diameter, 10:1–20:1) is used mainly as an asbestos replacement in construction and insulation board and automotive friction products, and in plastics and rubber. Powdered (milled) wollastonite, including small amounts of synthetic wollastonite, is used mainly in ceramics (the major current application of wollastonite) and in metallurgy.

Zeolites are crystalline aluminosilicate minerals with cagelike crystal structures. Zeolites have been used extensively since the 1940s in a variety of applications. Naturally occurring zeolites, some of which are fibrous, occur worldwide and many are used in materials for the construction industry, in paper, in agriculture, and in other applications. A large number of zeolites have been synthesized for use in detergents, as catalysts, and as adsorbents and desiccants. All available data on the following agents were considered: clinoptilolite, mordenite, phillipsite, nonfibrous Japanese zeolite, synthetic type A zeolite, and synthetic types 4A, MS 4A, and MS 5A zeolites.

Epidemiological studies on these agents, where available, were considered to be inadequate or of insufficient quality to allow an evaluation of their carcinogenicity in humans.

There was sufficient evidence in experimental animals for the carcinogenicity of long palygorskite (attapulgite) fibers (>5 µm) based upon studies in rats by inhalation and intrapleural and intraperitoneal administration. There was inadequate evidence in experimental animals for the carcinogenicity of short palygorskite (attapulgite) fibers (<5 µm). There was limited evidence in experimental animals for the carcinogenicity of long sepiolite fibers (>5 µm). There was inadequate evidence in experimental animals for the carcinogenicity of short sepiolite fibers (<5 µm). There was inadequate evidence in experimental animals for the carcinogenicity of wollastonite, clinoptilolite, mordenite, phillipsite, and nonfibrous Japanese and synthetic zeolites.

Consequently, long palygorskite fibers (>5 µm) were classified as possibly carcinogenic to humans (Group 2B), while short palygorskite fibers (<5 µm) could not be classified as to their carcinogenicity to humans (Group 3). All other materials evaluated, i.e., sepiolite, wollastonite, and some natural and synthetic zeolites (other than erionite), were also classified in Group 3 because the experimental studies provided only limited or inadequate evidence for carcinogenicity and epidemiological studies in humans were inadequate for evaluation or not available.

Other Agents

Two other agents were evaluated in the monographs series for the first time.

Coal is a generic term for a heterogeneous, carbonaceous rock of varying composition and characteristics. Coal typically contains variable but substantial amounts of mineral matter of which quartz is an important component. Exposure to coal dust occurs during mining, during bulk loading and transfer, and at sites where coal is stored and used, such as power stations, steel and coke works, chemical plants, and during domestic use.

There have been no epidemiological investigations on cancer risks in relation to coal dust per se. There is, however, a large body of published literature concerning cancer risks potentially associated with employment as a coal miner, including a small number of exposure–response associations with coal mine dust. Cancers of the lung and stomach have been investigated most intensively among coal miners, with sporadic reports for cancers of other sites such as urinary bladder. The absence of information on levels of the specific components of coal mine dust (e.g., coal, quartz, metals) hindered interpretation of the epidemiological literature. The evidence from occupational cohort studies for an association between coal mine dust and lung cancer has not been consistent; some studies revealed excess risks, whereas others indicated cohort-wide lung cancer deficits. There is no consistent evidence supporting an exposure–response relationship for lung cancer with any of the customary dose surrogates, including duration of exposure, cumulative exposure, or radiographic evidence of pneumoconiosis. In contrast to the lung cancer findings, there have been reasonably consistent indications of stomach cancer excess among coal miners, detected both in occupational cohort studies and in community-based case–control studies. However, there is no consistent evidence supporting an exposure–response gradient for coal mine dust and stomach cancer.

In experimental animals, coal dust was tested for carcinogenicity in two small studies in rats by inhalation and intrapleural injection. No increase in the incidence of tumors was observed.

The working group concluded that there was inadequate evidence in both humans and experimental animals for the carcinogenicity of coal dust. Coal dust could not be classified as to it carcinogenicity to humans (Group 3).

para-Aramid fibrils are long-chain synthetic polyamides, most commonly poly(*para*-phenyleneterephthalamide), produced commercially since the early 1970s. The combination of high strength, high temperature resistance, and light weight makes these fibers useful in the reinforcement of composite materials for the aerospace and sports equipment industries, in woven fabrics used in protective apparel, and in automotive brake pads and gaskets.

para-Aramid fibrils were tested for carcinogenicity in one study in rats by inhalation exposure. An increased incidence of cystic keratinizing squamous-cell carcinomas was reported. However, subsequent reexaminations and evaluation of these lesions revealed a diagnosis of pulmonary keratinizing cysts. The biological significance of these lesions is unclear. *para*-Aramid fibrils were also tested in two experiments in rats by intraperitoneal injection. No intra-abdominal tumors were observed.

There were no epidemiological data in humans exposed to *para*-aramid fibrils. It was concluded that there is inadequate evidence in experimental animals for the carcinogenicity of *para*-aramid fibrils and that *para*-aramid fibrils cannot be classified as to their carcinogenicity to humans (Group 3).

The resulting monographs, Volume 68 of the *IARC Monographs* series, will be published in May 1997.

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